Sildenafil-induced cardioprotection in rabbits

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In the August issue of this journal, Reffelmann and Kloner [1] reported the effects of sildenafil (Viagra) on myocardial infarct size following ischemia–reperfusion (I–R). These authors showed that pretreatment with 0.7 or 1.45 mg/kg of sildenafil prior to ischemia resulted in no protection against myocardial infarction. These findings are in contrast with a previous study from our laboratory[2] that demonstrated a significant reduction of infarct size in the rabbits pretreated with 0.7 mg/kg sildenafil. The reason for this disagreement is not clear, as stated by Reffelmann and Kloner[1] that “...the contradictory results largely remain unexplained, but emphasize that additional factors, due to subtle differences in the experimental model, might be able to modify the cardiovascular response to sildenafil...”. We are certainly puzzled by these negative findings, since the sildenafil-induced cardioprotection has been observed independently by a number of investigators in our laboratory by intravenous, intraperitoneal, and oral routes of the drug administration. Moreover, the infarct-limiting effect of sildenafil, first found in our in vivo rabbit model [2], has been recently confirmed in mice from our laboratory [3] and in rats by other investigators [4].

Indeed, it is difficult to explain the discrepancy between the findings of Reffelmann and Kloner [1] and our findings [2] because the in vivo rabbit models of regional I–R in these two studies appear to be almost identical, in terms of animal strain, anesthetics used, length of I–R, and infarct staining method. The only noticeable difference in the experimental procedure is that the drug infusion time (≈5 min) in their study was considerably longer than those in our study (≈1 min), which may potentially affect the hemodynamic response prior to ischemia. Unfortunately, a close comparison could not be made since these authors did not report the hemodynamic data for a 0.7 mg/kg dose in their paper [1]. In addition, the infarct size measurement for 0.7 mg/kg sildenafil-treated group was done only in five animals, instead of n = 12 (for 1.45 mg/kg group).

Based on our current knowledge of the mechanisms underlying preconditioning and myocardial protection, the sildenafil-induced protection makes good sense conceptually, also. Sildenafil is a selective inhibitor of phosphodiesterase type-5 (PDE-5), an enzyme that hydrolyses cyclic guanosine monophosphate (cGMP). Therefore, the direct inhibition of PDE-5 by sildenafil may result in a higher accumulation of cGMP in the heart tissue, which has been experimentally confirmed in sildenafil-treated rat myocardium [4]. cGMP has been shown to exert a number of actions that would be expected to be beneficial during myocardial ischemia [5–7]. Acute infusion of exogenous brain natriuretic peptide (BNP), which causes an increase in cGMP levels in ventricular myocardium, has been shown to be markedly protective against myocardial I–R injury in rat [8] and rabbit hearts [9]. cGMP may activate a protein kinase (PKG) that can subsequently open mitochondrial K ATP channels [10], leading to cardioprotection [2,11]. Also, a pharmacological opener of mitochondrial K ATP channels, diazoxide, has been shown to be cardioprotective in many animal species including the rabbit [12,13], although Hale and Kloner [14] failed to reproduce its protective effect in their rabbit model of myocardial infarction. Furthermore, our mouse study [3] has demonstrated that sildenafil-induced delayed preconditioning is mediated by nitric oxide (NO), which could activate soluble guanylyl cyclase, an enzyme that converts GTP to cGMP resulting in the increase in cGMP tissue level. Our results are also in accordance with a recent study showing that enhanced synthesis of cGMP is required for protection in delayed ischemic preconditioning in rabbit hearts [15]. Therefore, the results reported by Reffelmann and Kloner [1] appear to be inconsistent with the existing mechanistic paradigm.

It is our belief that our published studies in rabbits [2] and mice [3] and ongoing investigations into the in-depth
signaling pathways in sildenafil-induced cardioprotection should provide novel insights into the potential use of sildenafil for treating ischemia–reperfusion injury. Also, it is encouraging to note that recent human studies have demonstrated the beneficial effects of sildenafil therapy in the treatment of pulmonary hypertension [16–18] and heart failure [19]. The controversy surrounding sildenafil-induced cardioprotection will eventually be resolved when more, new data emerge from other independent investigators around the world.

References


